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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/346,794	07/02/1999	TERRY P. SNUTCH	NMEDP001-2	2888

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EXAMINER	
BASI, NIRMAL SINGH	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 01/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/346,794	SNUTCH ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *25-40* is/are pending in the application.

4a) Of the above claim(s) *33,34,36,37,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *25-32,35 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/18/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Amendment filed 10/18/04 has been entered. Applicant has added new claims 32-40. Claims 25-31 were previously presented. Claims 1-24 were previously cancelled.

2. Applicant argues because the examiner has used the word species in a previous Office Action that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141, as indicated on the last paragraph on page 3 of the December 31, 2002 Office action.

Claims pertaining to assaying the distinct polypeptide encoded by SEQ ID NO:23 will be examined. Therefore claims 25-31, in so far as they encompass SEQ ID No:23 will be examined. Claims 32, 35, and 38 will also be examined because they pertain to SEQ ID NO:23. Claims 33-34, 36-37, and 39-40 will not be examined, nor will they be rejoined when the base claim is allowed.

Applicants elected the SEQ ID NO: 23 (January 31, 2003). Applicants' election was in response to the Office Action mailed 31 December 2002. In the paper filed 3/26/04 Applicants provisionally elected, with traverse, claims directed to the use of the α1 subunit encoded by a nucleotide sequence that hybridizes to a nucleic acid comprising SEQ ID NO: 23 . The claims were properly restricted between the three nucleic acid sequences specified in each independent claim.

Examiner has briefly recited the timeline of Restrictions imposed by the office and also indicated Applicants responses:

On 10/4/00, Office mailed Restriction requirement

On 12/8/200, Applicants elected Group XVI, claim 21, directed to a screening method.

On 10/8/02 Applicant amended the pending claims, to overcome Examiner's rejections. Applicants amended the claims to read on a method for identifying a compound which behaves as an agonist for a T-type calcium channel which is encoded by a nucleotide sequence which hybridizes to a nucleic acid comprising SEQ ID NO:23, 25, or 27.

On 31 December, 2002, in response to Applicant's Amendment, the Examiner further restricted the claims. The office action specifically stated, "The nucleic acid comprising SEQ ID NO: 23, 25 or 27 are three distinct classes of calcium channel subunits and constitute recitation of an implied, mis-joined Markush group that contains multiple, independent and distinct inventions. Each of the different nucleic acids encode a distinct polypeptide with distinct structural or functional properties and therefore the methods of their use are independent and distinct". It was also stated, "**This requirement is not constructed as a requirement for election of species since each of the compounds recited in alternative form is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention,**

On 2nd February, 2003, Applicant elected SEQ ID NO:23 with traverse. The Examiner further stated, " The previous restriction requirement was not

meant to be constructed as a requirement for election of species". Therefore, further emphasizing the requirement, "**This requirement is not constructed as a requirement for election of species since each of the compounds recited in alternative form is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention**", as stated in the previous Office action.

On May 6, 2003 the Examiner acknowledged Applicants election, with traverse, of the species of nucleic acid comprising SEQ ID NO:23. Applicants' arguments were fully considered but not found persuasive. The requirement was deemed proper and therefore made FINAL.

Based on the above responses by the Office restriction was proper.

Therefore, the use of each individual nucleic acid comprising SEQ ID NO:23, 25 or 27 is considered distinct. Therefore, the restriction requirement is not to be construed as a requirement for election of species, since each of the compounds recited in alternative form is not a member of a single genus of invention, but constitutes an independent and patentably distinct invention; therefore the use of each member in a method also constitutes an independent and patentably distinct invention. The claims of elected Group XVI are drawn to a method to identify a compound which behaves as an agonist or an antagonist for a T-type calcium channel by contacting the α_1 subunit of a heterologous T-type calcium channel with a compound, wherein said α_1 subunit is encoded by a nucleotide sequence which hybridizes (under conditions of specific stringency) to a nucleic acid comprising SEQ ID NO:23, 25 or 27. The claims apply to

numerous T-type calcium channel α_1 subunits. The nucleic acid comprising SEQ ID NO:23, 25 or 27 are three distinct classes of calcium channel subunits, each an independent and distinct invention. Each of the different nucleic acids encodes distinct polypeptides with distinct structural or functional properties, each one with different agonist or antagonist binding properties. Agonists or antagonists identified, for example, by the use of the polypeptide encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO:23, may not be the same as those identified by the polypeptide encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO:25 or 27. The nucleic acids comprising SEQ ID NO:23, 25 and 27 were grouped into distinct Groups III, IV and V respectively, in paper number 8 (10/4/000). Therefore, the use of each individual nucleic acid comprising SEQ ID NO:23, 25 or 27 is also considered distinct. The nucleic acids of Groups III-V are distinct for reasons of record, see paper number 8. Accordingly, these claims are subject to restriction under U.S.C.§ 121. Further a search of SEQ ID NO:23, 25 and 27 and all the possible nucleic acids that would hybridize to said nucleic acid and encode a T-type calcium channel would not be co-extensive particularly with regard to the literature search. An examination of the materially different, patentably distinct inventions in a single application would constitute a serious undue burden on the examiner. The requirement is still deemed proper and is therefore still FINAL.

3. Applicants argue the claimed methods have well-established, specific, substantial and credible utilities and the specification teaches such uses. Applicants arguments have been fully considered but not found persuasive, and

are addressed below. Applicant's arguments have been fully considered but are not found persuasive.

Examiner's Response to Applicants' Arguments Pertaining to Rejection Under, 35 U.S.C. 101 and 112, first paragraph

4. Claims 25-31 remain rejected, under 35 U.S.C. 101 and 112, first paragraph, for reasons of record in the Office Action dated 5/6/03, 2/7/02 and, 6/14/04 for the reasons given below. Newly added claims 32, 35 and 38 are also rejected under 35 U.S.C. 101 and 112, first paragraph, for the same reason as those applied to claims 25-31, said reasons are disclosed in the Office Action dated 6/14/04, 5/6/03, 2/7/02 and for the reasons given below.

Applicants' argue present claims are not directed to treating diseases but are directed to identifying compounds that are likely to be useful in treating disease conditions. Examiner agrees the claims are directed to identifying compounds that interact with T-type calcium channels and interfere with the flow of calcium. The question is, if a compound is found to interact with the T-type ion channel of SEQ ID NO:23 what disease will it treat?. It may not treat any disease. Further experimentation is required to determine the effectiveness of the compound identified. Applicant states "identifying compounds that are likely to be useful in treating disease conditions". Just because a compound affects the ion channel does not mean it is likely to treat a disease. There is no disclosure that agonists for the T-type ion channel of SEQ ID NO:23 will be beneficial for a particular dysfunction. What is to say an antagonist may not be beneficial. Both

agonists and antagonists may be useless in treatment of a disease. The T-type ion channel of SEQ ID NO:23 may be integral polypeptide required for normal functioning of the cell. Therefore interfering with its activity may be detrimental to the cell. In that case all agonists and antagonists may be useless for manipulation of said ion channel. Applicants argue that page 9 of the specification discloses conditions associated with calcium channels are namely epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease. As such, agonists or antagonists identified by the claimed methods may be used to treat such conditions. The statement that disease states such as epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease can be associated with calcium channels may be true but the question is what specific disease state is associated with dysfunction of the ion channel of SEQ ID NO:23. No one calcium channel has been identified that results in all of the diseases disclosed on page 9. The specific dysfunction associated with T-type ion channel of SEQ ID NO:23 is not known or disclosed in the prior art. Therefore what is the utility for a compound that is an antagonist or agonist for said channel. Are agonists beneficial or detrimental for treating a disease condition. Are antagonists beneficial or detrimental for treating a disease condition. Is increased activity of the channel beneficial? Is decreased activity of the channel beneficial? The specifcation provides no answers with regard to the T-type ion channel of SEQ ID NO:23. Therefore further experimentation is

required to assign a utility the channel. Also further experimentation is required assign a utility to any compound than may be shown to be an agonist or antagonist of T-type ion channel of SEQ ID NO:23.

Further the not a single compound has been isolated by the claimed method that treats a specific disease.

Applicant argues agonists and antagonists identified by the methods of the invention are useful as having an effect on the activity of calcium ion channels. In turn, such agonists and antagonists are useful in treating conditions identified in

the specification. Applicant's arguments have been fully considered but not found persuasive. Ethanol in increasing concentrations will antagonize the flow of calcium though the T-type ion channel of SEQ ID NO:23. To follow applicant's line of thinking, ethanol therefore must be useful for treating conditions identified in the specification. The conditions identified in the specification are epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome and Parkinson's disease. The examiner is not aware of any art that even remotely suggests that ethanol will treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina,.

Further applicant argues the office appears to have ignored the precedence of at least two patents that have issued directed to nucleotide sequences encoding T-type calcium channels. These patents are U.S. Patent Nos. 6,358,706 and 6,309,858. Based on the issuance of these patents the T-

type calcium channels are argued to be useful as presently claimed. Applicants' reference to issued Patents as establishing a patentable utility for the claimed protein is not persuasive because each application is examined on its own merits. In the decision of *In re Hutchison*, 69 USPQ 138 (CCPA, 1946), the court held that

> "We are not concerned, of course, with the allowed claims in either the patent or in this application. The sole question for our determination is whether the six article claims on appeal were properly rejected below, and this we pass upon without further reference to, and without comparing them with, the claims in the patent or the claims, which stand allowed in this application."

In essence, the position in the instant application that each application is examined on its own merits can be found in the judicial precedent cited above. The rejections in the instant application will only be withdrawn if they are shown to be legally or factually unsound.

In conclusion:

Applicant argues that the Office alleges that there is no disclosure that Mg^{2+} or N^{2+} can treat variety of diseases associated with ion channel activity. It is not clear how these ions relate to the claimed methods which are directed to identifying a compound in claims 25, 28, and 31, and those claims dependent thereon. The Examiner was arguing that all compounds identified by claimed method are not directly useful but require further experimentation. To put it perspective Applicant argues agonists and antagonists identified by the methods of the invention are useful as having an effect on the activity of calcium ion channels. In turn, such agonists and antagonists are useful in treating conditions

identified in the specification. It has been shown (see previous Office Action) Ni^{2+} blocks T channels, but as stated by Sylvie (page 37, column 3), "It is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Since Ni^{2+} blocks T channels, it may block T-type calcium channel of SEQ ID NO:23, if it does then does it mean that it (antagonist) will be useful in treating all the conditions identified in the specification?

There is no showing in the prior art or specification that agonists and antagonists identified by the claimed screening assays are useful for treating diseases including, epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease. Although the T-type calcium ion channel of SEQ ID NO:23 may be involved in one or more of the aforementioned disease states further experimentation is required to determine which disease state, if any, is a result of said T-type calcium ion channel dysfunction. Just because a nucleic acid hybridizes to the polynucleotide of SEQ ID NO: 23 it does not automatically mean it will encode a protein that will be involved in the aforementioned disease states. Again further experimentation is required to determine a function. Further, there is no disclosure of even a single agonist or antagonist identified by claimed method that will act as an antagonist or agonist to treat the diverse diseases claimed as possible targets. There is no disclosure of whether an agonist as compared to an antagonist will treat a specific disease. Therefore, further experimentation is required to find a compound that will bind to the T-type calcium ion channel used in instant methods and correlate it with a disease state.

Claims 25-27 are directed to method for identifying agonists for a T-type calcium channel. Applicants have not disclosed a single agonist that has been identified by claimed method. Also the art provided by Applicants does not disclose a single compound that behaves as an agonist in the claimed method. Applicants have relied only on antagonists to argue utility.

Prior art does not disclose a utility for claimed invention, it argues to the contrary. The biophysical and pharmacological properties of T-type calcium channels are varied and their function is unknown. Although, the claimed method for identifying agonists and antagonists is considered useful by the Applicants, under 35 U.S.C. 101, they are not considered to have utility. What is the utility for method for identifying agonist and antagonist for a T-type α_1 subunit whose biophysical and pharmacological properties and function is unknown? The critical feature of the invention is the identification of compounds that activate or inhibit specific α_1 subunits of T-type Ca^{2+} channels. Since the α_1 subunits of T-type Ca^{2+} channels encoded by the polynucleotide of SEQ ID NO: 23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 are not considered to have utility under 35 U.S.C. 101, the method of their use is also are not considered to have utility.

The state of the prior art is disclosed in the review article of Sylvie et al (Sylvia et al, 1997, TIPS, Vol. 18, pages 37-42). Sylvie states, "Among Ca^{2+} channels, the low-voltage-activated T-type Ca^{2+} channel (T channel) is probably the most atypical. It was first described in 1984 and is found in a variety of cells where its precise role remains to be established. In addition, its molecular

structure has never been defined, despite numerous attempts to sequence and clone it", page 37, first column. Sylvie does acknowledge that new drugs are being developed, which may block T-type channels. The drugs tested so far have not been shown to treat a single disease state, let alone the laundry list of diseases cited by applicants. Sylvie discloses the electrophysiological and pharmacological properties of T-type channels are varied (Table 1), and all T channels rarely meet the electrophysiological criteria (page 37, column 2). The effect of compounds on the ion channel is extremely dependent not only on the alpha-subunit but also on that of the associated beta-subunits (Sylvie et al, page 37, column 3). Therefore, the actions of compounds on T-type calcium channels depend on the molecular composition of the expressed channels and on the experimental conditions (Sylvie et al, page 37, column 3). The associated beta or other subunits required for a specific function of the T-type channel protein encoded by the nucleic acid of SEQ ID NO: 23 and the ion channels encoded by a nucleotide, which hybridizes to the nucleic acid of SEQ ID NO: 23, in claimed method, are not disclosed. A compound that acts as an agonist or antagonist on the $\alpha 1$ T-type channel protein used in claimed method may not have the same effect on other $\alpha 1$ T-type channel proteins. For example Ni^{2+} blocks T channels, but as stated by Sylvie (page 37, column 3), "It is difficult to predict the actual potency of Ni^{2+} block and it is risky to rely on it to classify an expressed channel as T-type. Sylvie also discloses, many antagonists have been discussed as possible pharmacological markers of T channels (tetrandrine, ethosuximide, phenytoin, zonisamide, U920320) but none are selective or potent enough to be

useful (page 38, column 2). Many drugs may block calcium channels but none are available that are selective in blocking T channels (Sylvie et al, page 38, column 3). Further, compounds may have different effects depending on their concentration. For example, Sylvie discloses the effect of different Ca^{2+} channel antagonists and states, "Nifedipine (<100 nm) increased aldosterone secretion while higher concentrations reduced it". Other agents that have been shown to interact with T-type channels are mibefradil, Mg^{2+} and Ni^{2+}. Although the claimed method can identify agents that may enhance or reduce the flow of ions into a cell expressing the α_1 subunit of a functional T-type calcium ion channel, neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the disclosed result. For example there is no disclosure that Mg^{2+} or Ni^{2+} can treat epilepsy, migraine, ataxia, schizophrenia, hypertension, arrhythmia, angina, depression, small lung carcinoma, Lambert-Eaton syndrome, and Parkinson's disease associated with interfering with ion channel activity of the α_1 subunit of a functional T-type calcium ion channel. Further there is no disclosure if agonists would be beneficial for treatment of a dysfunction associated with α_1 subunit of T-type calcium ion channel or if antagonists would be beneficial for treatment of said dysfunction. Also, the prior art teaches that the entry of calcium through voltage-dependent Ca^{2+} channels in neurons controls diverse functions, such as neurotransmitter release, excitability, and differentiation (Williams et al, 1992, Neuron, Vol. 8, see page 71, column 2). Other diverse effects of compounds on Ca^{2+} channels are disclosed throughout the Review Article of Sylvie.

The utilities asserted by Applicant are not substantial or specific. Neither the specification nor the art of record disclose any disease states treatable by the agonists and antagonists identified by the method of instant invention. Similarly, neither the specification nor the art of record disclose any instances where blocking any effects of T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 would reduce the effect of a disease state. Thus the corresponding asserted utilities are essentially methods of treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use, especially, when the $\alpha 1$ subunit of the T-type calcium channel encoded by the a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23 of the claimed invention is not known. Since neither the specification nor the art of record disclose any activities or properties that would constitute a "real world" context of use for the disclosed polynucleotides/polypeptides/ agonists/antagonists, further experimentation is necessary to attribute a utility for the method of using the disclosed T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO:23 or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO:23. See Brenner v. Manson, 383 U.S. 519, 535-36, 148 USPQ 689, 696 (1966) (noting that "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of

use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Since the utilities asserted by Applicant for the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23, are not substantial or specific, then it follows that the method of claims 25-31, 32, 35 and 38 (method of identifying compounds capable of acting as agonists or antagonists for T-type mammalian calcium channels), also has no utility. No specific disease state has been shown to result from dysfunction of the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23. Similarly, agonists and antagonists identified by said method have no utility in treatment of disease that result from dysfunction of the T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23.

A utility to T-type calcium ion channel encoded by the polynucleotide of SEQ ID NO: 23, or ion channel encoded by a polynucleotide which hybridizes to the nucleic acid of SEQ ID NO: 23, cannot be assigned without knowledge of what disease is associated with ion channel dysfunction or what drugs/ligands effect a specific function associated with said dysfunction. The superfamily of calcium ion channels is highly divergent in their effects and compound specificity. The utility of α_1 subunits T-type Ca^{2+} channels of instant invention cannot be

implicated solely from homology to known ion channels or their protein domains. The art does not provide any teaching stating that all members of the family calcium ion channels must have the same effects, the same ligands and be involved in the same disease states. The art discloses evidence to the contrary. The specification has used protein domains/homology are predictive as to the activity of the protein. The utility of claimed α_1 subunits T-type Ca^{2+} channels cannot be implicated solely from homology to known ion channels or their protein domains because the art does not provide any teaching stating that all members of the family of ion channels must have the same effects, the same ligands, transport the same compound and be involved in the same disease states. The art discloses evidence to the contrary (see above).

Bork (Nature Genetics, Vol. 18, pages 313-318, 1998) provide a review article disclosing the problems of using homology detection methods to assigning function to related members of a family. Bork discloses: a) "While current homology detection methods can cope with data flow, the identification, verification and annotation of functional features need to be drastically improved", page 313, column 1, Abstract, b) there are two bottle necks that need to be overcome en route to efficient functional predictions from protein sequences, i.e., "First, there is the lack of a widely accepted, robust and continuously updated suite of sequence analysis methods integrated into coherent and efficient prediction system. Second, there is considerable 'noise' in the presentation of experimental information, leading to insufficient or erroneous function assignment in sequence databases", page 313, column 1, third paragraph, c) "In-depth

analysis of protein sequences often results in functional predictions not attained in the original studies", page 313, column 2, last paragraph, d) "However, more often than not, it is clear that the cellular role of the protein in question differs from that of the detected homologue(s) and there is currently no automatic means to establish how much functional information can be legitimately transferred by analogy from homologue to the query", page 315, column 2, last paragraph, e) pertaining to predictions of protein function, "Do not simply transfer functional information from the best hit. The best hit is frequently hypothetical or poorly annotated; other hits with similar or even lower scores may be more informative; even the best hit may have a different function", while "many proteins are multi-functional; assignment of a single function, which is still common in genome projects, results in loss of information and outright errors" and "It is typical that the general function of a protein can be identified easily but the prediction of substrate specificity is unwarranted; for example, many permeases of different specificity show approximately the same level of similarity to each other", page 316. Karp (Bioinformatics, Vol. 14, No.9, pages 753-754, 1998) has disclosed the problems of using functional prediction based on homology analysis. Karp states, a) "Although we know the accuracy with which sequence homologs can be determined, we know little about the accuracy of the overall process of assigning function by homology, page 753, column 2, second paragraph, b) "We have more faith in the correctness of those sequences whose functions we determined experimentally, rather than through computational means, page 753, column 2, last paragraph, c) "research is required to estimate

the error rate of functional annotation by different methods of computational sequence analysis", page 754, column 2, last paragraph. Bork (Current Opinion in Structural Biology, Vol. 8, pages 331-332, 1998), discusses the problems with deriving biological knowledge from genomic sequences and states, "structural similarity does not lead to iron-clad functional predictions" page 331, column 2 last paragraph, "Structural similarity does not necessarily mean a common evolutionary origin" page 332, column 1, second paragraph, and "Today, what we predict from sequences is at best fragmentary and qualitative", page 332, column 2, second paragraph. Therefore, references discussed above disclose the unpredictability of assigning a function to a particular protein based on homology, especially one that belongs to the family of Ca^{2+} channels, which have very different ligand specificity and functions.

1) The α_1 subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23, 25 or 27 may be full-length subunits. The specification does not teach a person of ordinary skill in the art how to use the specified α_1 subunit in screening assays so that they meet the utility requirements under 35 U.S.C. 101, as indicated above. The specification also does not teach a person of skill in the art how to use the specified α_1 subunit in screening assays so that they meet "how to use" requirement under 35 U.S.C. 112, first paragraph.

2) Publications at the time the priority application was filed do not demonstrate the α_1 subunit encoded by nucleotide sequences that hybridize to a nucleic acid comprising SEQ ID NO: 23, 25 or 27 had a well-established utility,

and there was no showing that all agonists and antagonists interacted with all T-type calcium channels. Also there was no showing all agonists and antagonists, or even one could be used to treat diseases of hypertension, stroke, epilepsy, heart disease and cancer.

3) The declaration submitted by Dr. Snutch, has been fully considered by the Office, but it does not demonstrate the claimed screening methods are useful for identifying molecules that treat specific T-type calcium channel related diseases.

4). Due to the facts delineated in items 1, 2 and 3, the screening assays do not have a well-established, specific, substantial and credible utility for identifying compounds useful for treating diseases enumerated in the specification.

5) Extensive experimentation is required beyond the claimed processes to identify compounds that treat diseases listed in the specification.

6. Even if the Office already has allowed Patents directed to T-type channels, said Patents cannot be used to establish utility.

Therefore, claims 25-31, 32, 35 and 38 are rejected under 35 U.S.C. 101/35 U.S.C. 112, first paragraph, for reasons of record and those provided above. Claims 25-31 32, 35 and 38 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims remain 25-31, 32, 35 and 38 are rejected under 35 U.S.C. 112, first paragraph (for reasons of record and those provided above). Specifically,

since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicant is advised that claims 25-31 are directed to non-elected invention of the nucleic acid of SEQ ID NOs:25 and 27 and must be amended.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nirmal S. Basi whose telephone number is 571-272-0868. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa can be reached on 571272-0829. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nirmal S. Basi
January 24, 2005

MICHAEL PAK
PRIMARY EXAMINER